Exhibit 5

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE: NATIONAL PRESCRIPTION OPIATE LITIGATION	)	MDL No. 2804
This document relates to:	)	Case No. 17-md-2804
The County of Cuyahoga v. Purdue Pharma L.P., et al., Case No. 17-OP-45004 (N.D. Ohio)	)	Hon. Dan Aaron Polster
The County of Summit, Ohio, et al. v. Purdue Pharma L.P. et al., Case No. 180OP-45090 (N.D. Ohio)	)	

REPORT OF CARL C. PECK, M.D.

the safety and efficacy of Vicodin aided in its determination of safety and efficacy with respect to Norco. The application approval materials for ANDA 040148, for example, stated: "The drug product, Hydrocodone Bitartrate and Acetaminophen Tablets USP, 10 mg/325 mg (Norco) can be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness."[71]

VII. THE FDA'S ONGOING OVERSIGHT

A. The FDA has long regulated and permitted the use of prescription opioids; it continues to approve new prescription opioids.

The FDA has long regulated and monitored prescription opioid pain medications, including their misuse and abuse. In fact, the FDA maintains a webpage, which it regularly updates, setting out in timeline form its many "Activities and Significant Events Addressing Opioid Misuse and Abuse."[72] The FDA's timeline begins in 1911, with most events beginning in the early 2000s and continuing into 2019.[73]

The FDA's actions recognize—and work to mitigate—the risks of addiction, overdose, misuse and abuse.[74] These include, among many others, the Opioid Analgesics Risk Evaluation and Mitigation Strategies ("REMS") (*see infra* § X) and labeling changes (*see infra* § IX). They also demonstrate the FDA's continued recognition of the important role that opioids can play in the proper treatment of pain by physicians and other

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[71] ALLERGAN_MDL_04161107 at -1110; *see also* ALLERGAN_MDL_04161181 at -1184 (stating, with respect to ANDA 040099, that the FDA had determined that the medication could "be expected to have the same therapeutic effect as that of the listed drug product upon which the Agency relied as the basis of safety and effectiveness").

[72] *See* FDA Webpage re *Timeline of Selected FDA Activities and Significant Events Addressing Opioid Misuse and Abuse*, available at https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM566985.pdf (hereinafter "FDA Timeline").

[73] *Id.*

[74] *Id.*

prescribers.[75] For example, the FDA has found that, "[w]hen prescribed and used properly, opioids can effectively manage pain and alleviate suffering—clearly a public health priority."[76] In support of this finding, the FDA has observed that "[c]hronic pain is a serious and growing public health problem: it 'affects millions of Americans; contributes greatly to national rates of morbidity, mortality, and disability; and is rising in prevalence.'"[77] In addition, the FDA has recognized that there is evidence that pain is inadequately treated.[78] The FDA states on its website that, "[a]ccording to the National Institutes of Health, studies have shown that properly managed medical use of opioid analgesic compounds (taken exactly as prescribed) is safe, can manage pain effectively, and rarely causes addiction."[79]

Evidencing that the FDA continues to believe that the benefits of opioids outweigh their risks, the FDA continues to approve New Drug Applications for opioid pain medications, including extended-release formulations and hyper-potent versions. In the last five years, the FDA has approved the following, among others:[80]

- **November 20, 2014:** Hysingla ER, extended-release hydrocodone bitartrate.

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[75] *Id.*

[76] Sept. 10, 2013 Response to PROP Citizen Petition, at 2, available at http://www.supportprop.org/wp-content/uploads/2014/12/FDA_CDER_Response_to_Physicians_for_Responsible_Opioid_Prescribing_Partial_Petition_Approval_and_Denial.pdf (hereinafter "FDA Response to PROP Petition").

[77] *Id.* (quoting Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research, Committee on Advancing Pain Research, Care, and Education; Institute of Medicine, 2011:1-364).

[78] *Id.*

[79] *See* FDA Webpage on *A Guide to Safe Use of Pain Medicine*, available at https://www.fda.gov/consumers/consumer-updates/guide-safe-use-pain-medicine; Lembke Dep. Ex. 21.

[80] *See* FDA Timeline.

- **October 2, 2015:** MorphaBond, extended-release morphine sulfate (like Kadian®).
- **April 26, 2016:** Xtampza ER, extended-release oxycodone.
- **April 20, 2017:** RoxyBond, immediate-release oxycodone hydrochloride.
- **November 2, 2018:** Dsuvia, a sufantenil sublingual tablet, an extremely potent opioid, 10 times stronger than fentanyl, for use in limited circumstances.[81]

The approval process, however, is not the end of the story. If the FDA subsequently determines that the benefits of a medicine do not outweigh the risks, the FDA can request that application holder remove the medicine from the market. The FDA can also withdraw its approval of the medication.[82] Among the reasons that the FDA may withdraw approval are when the FDA finds that "clinical or other experience, tests, or other scientific data show that the drug is unsafe for use under the conditions of use upon the basis of which the application or abbreviated application was approved," that "new evidence of clinical experience, not contained in the application or not available to the FDA until after the application or abbreviated application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when the application or abbreviated application was approved, evaluated together with the evidence available when the application or abbreviated application was approved, reveal that the drug is not shown to be safe for use under the conditions of use upon the basis of which the application or abbreviated application was approved," "[u]pon the basis of new information before FDA with respect to the drug, evaluated together with the evidence available when the application or

[81] *See* FDA Approval Letter for Dsuvia, available at https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/209128Orig1s000Ltr.pdf.
[82] 21 C.F.R. § 314.150 ("Withdrawal of approval of an application or abbreviated application.").

abbreviated application was approved, that there is a lack of substantial evidence from adequate and well-controlled investigations as defined in 314.126, that the drug will have the effect it is purported or represented to have under the conditions of use prescribed, recommended, or suggested in its labeling," or "[t]hat the application or abbreviated application contains any untrue statements of a material fact."[83]

B. The FDA has imposed Postmarketing Requirements to further study and monitor the risks and benefits of prescription opioids.

In 2007, Congress amended the Federal Food, Drug, and Cosmetic Act, giving the FDA power to require postmarketing requirements ("PMRs").[84] Specifically, the FDA was given the power to "require … a postapproval study or studies of the drug, or a postapproval clinical trial or trials of the drug."[85] Postapproval studies or clinical trials are authorized where the FDA becomes aware of "new safety information," defined as "a serious risk or an unexpected serious risk associated with use of the drug that the [FDA] has become aware of … since the drug was approved, since the risk evaluation and mitigation strategy was required, or since the last assessment of the approved risk evaluation and mitigation strategy for the drug," or "the effectiveness of the approved risk evaluation and mitigation strategy for the drug obtained since the last assessment of such strategy."[86]

The purpose of a postapproval study or clinical trial is (i) "[t]o assess a known serious risk related to the use of the drug involved"; (ii) "[t]o assess signals of serious risk related to the use of the drug"; and (iii) "[t]o identify an unexpected serious risk when available data indicates the potential for a serious risk."[87] To meet these goals, the FDA

[83] *Id.* at § 314.150(a)(2).
[84] 21 U.S.C. 355(o).
[85] 21 U.S.C. 355(o)(3)(A).
[86] 21 U.S.C. § 355-1(b)(3); *see* 21 U.S.C. § 355(o)(3)(C).
[87] 21 U.S.C. § 355(o)(3)(B).

must first require a postapproval study; only if the FDA concludes that a study would not be sufficient to meet these goals may the FDA require a postapproval clinical trial.[88]

As explained below, in its September 10, 2013 response to a Citizen Petition filed by a group called the Physicians for Responsible Opioid Prescribing ("PROP") (*see infra* § VII.C), the FDA stated that, pursuant to its enhanced authority under the Federal Food, Drug, and Cosmetic Act, it was requiring NDA sponsors of extended-release, long-acting opioids to conduct PMRs "to assess certain known serious risks of ER/LA opioid use: misuse, abuse, hyperalgesia, addiction, overdose, and death."[89]

That same day, the FDA sent a letter to Watson Laboratories, Inc. (the former Allergan affiliate that held the Kadian® NDA at the time) notifying the company that the FDA would be requiring PMRs, based in part on the PROP Petition. Specifically, the FDA stated that it "has concluded that more data are needed regarding the serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of [extended-release long-acting] opioid analgesics."[90] The FDA's letter contained a list of five PMRs, including studies to provide quantitative estimates of the serious risks of opioids associated with long-term use, studies designed to define and validate "doctor/pharmacy shopping" as outcomes of misuse, abuse, or addition, and a clinical trial to estimate the risk of developing hyperalgesia following use of long-acting opioids.[91] In response, Actavis and several other opioid manufacturers entered into an agreement "to

[88] 21 U.S.C. § 355(o)(3)(D)(ii).
[89] FDA Response to PROP Petition at 1-2.
[90] ALLERGAN_MDL_01291325.
[91] *Id*.

effectuate their collaboration to complete the PMRs."[92] The agreement's signatories are known as the Opioid PMR Consortium ("OPC").[93]

A few months later, in April 2014, the FDA announced a public stakeholder meeting to gain insight into the design and conduct of the PMRs.[94] The FDA sought insight on these issues from stakeholders, including patients, academics, researchers, government regulators, healthcare organizations, the pharmaceutical industry, and the general public.[95] Subsequently, the FDA withdrew the original five PMRs and replaced them with eleven PMRs, namely ten studies and one clinical trial.[96]

Several of the PMRs, including the clinical trial, remained ongoing as of May 2019. These studies and trial as well as others of their type are another tool in the FDA's toolbox for its continuing oversight and regulation of these medications, including their risks.

C. **The FDA has considered a number of opioid-related Citizen Petitions.**

Responses to Citizen Petitions are another way in which the FDA has regulated and overseen prescription opioid medications. A Citizen Petition is a formal mechanism whereby concerned citizens or organizations can provide views, data on a medicine's safety or other relate matter, along with recommendations for FDA actions.

Federal regulations provide for the format, content and submission of Citizen Petitions.[97] FDA regulations, policies, pending or past decisions are all candidate subjects for public critique, comment, and request for modification via the Citizen Petition rules

[92] ALLERGAN_MDL_02342317.
[93] *Id*.
[94] *See Public Meeting; Request for Comments - Postmarketing Requirements for the Class-Wide Extended-Release/Long-Acting Opioid Analgesics*, available at https://www.regulations.gov/document?D=FDA-2014-N-0374-0001.
[95] *Id*.
[96] ALLERGAN_MDL_02023773.
[97] 21 C.F.R. § 10.3.

and procedures. Citizen Petitions and FDA's responses are open to the public and are maintained in an electronically accessible docket. FDA is required to carefully review and respond to each Citizen Petition within 180 days of receiving it. FDA responses to Citizen Petitions reveal FDA's view on the issues raised by each Petition.

There have been a number of Citizen Petitions relating to opioid pain medications. Notably, Physicians for Responsible Opioid Prescribing ("PROP")—an organization led by one of Plaintiffs' disclosed experts (who I understand was subsequently withdrawn by Plaintiffs), Dr. Jane Ballantyne, and which includes on its Board of Directors another proffered expert, Dr. Anna Lembke—submitted a three-page Citizen Petition on July 26, 2012.[98] The Petition outlined several of the group's concerns:

> (a) "[T]he FDA-approved indication for nearly all instant-release opioid analgesics is "moderate to severe pain." For extended-release opioids, the indication is for "moderate to severe pain when a continuous, around-the clock analgesic is needed for an extended period of time."
>
> (b) "These overly broad indications imply a determination by FDA that they are safe and effective for long-term use."
>
> (c) "[A]n increasing body of medical literature suggests that long-term use of opioids may be neither safe nor effective for many patients, especially when prescribed in high doses."

On the basis of these stated concerns, the PROP Citizen Petition requested FDA to modify the current labels of opioid analgesics as follows:

[98] *See* July 25, 2012 PROP Citizen Petition, available at https://www.citizen.org/sites/default/files/2048.pdf (hereinafter "PROP Petition").

1. "Strike the term 'moderate' from the indication for non-cancer pain.""

2. "Add a maximum daily dose, equivalent to 100 milligrams of morphine for non-cancer pain."

3. "Add a maximum duration of 90-days for continuous (daily) use for non-cancer pain."

After receiving the petition, the FDA solicited information and comment from the public. In response to the PROP Citizen Petition, the FDA received over 1,900 comments.[99] Some public health agencies and organizations supported the Petition due to concerns over increased opioid abuse; however, most commenters opposed PROP's requests, including the American Medical Association, the American Society of Anesthesiologists, and several patient advocacy groups. Those in opposition expressed concern that the labeling changes recommended were not supported by scientific evidence, and the proposed uniform approach to maximum dosage and duration of treatment was inconsistent with the need for individualized treatment and the variability among patient responses to opioids.[100]

After receiving these comments, the FDA responded in detail to the PROP Citizen Petition on September 10, 2013, denying the Petition in large part.[101] Despite PROP's requests, the FDA declined to take, among others, several actions. *First*, while PROP had requested a maximum daily dose of the equivalent of 100 milligrams of morphine, the FDA specifically declined to "specify or recommend a maximum daily dose or duration of use

[99] FDA Response to PROP Petition at 5
[100] *Id*.
[101] Id.

for any opioid."[102] In so determining, the FDA found that Dr. Lembke's PROP group's cited "scientific literature does not support establishing a maximum recommended daily dose of 100 mg MED," rejecting PROP's contention that it did.[103] For example, the FDA stated that while "the available data do suggest a relationship between increasing opioid dose and risk of certain adverse events," "the available information does not demonstrate that the relationship is necessarily a causal one."[104] Thus, although PROP had "selected a 90-day limit," PROP had "provide[d] no evidence that addiction (however it is defined) increases significantly after 90 days of use such that it would support a labeling change."[105]

Second, the FDA rejected Dr. Lembke's group's request that the FDA "[a]dd a maximum duration of 90 days for continuous (daily) use."[106] As support for this contention, PROP had argued that "[l]ong-term safety and effectiveness of managing [pain] with opioids has not been established."[107] But the FDA said that PROP's request was "not supportable."[108] In so concluding, the FDA examined the materials cited by Dr. Lembke's group and found them lacking. Critically, the FDA stated that "[t]he cited literature does not identify a duration threshold beyond which the risk of addiction outweighs the benefits of opioid treatment."[109]

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[102] *Id.* at 11-14.
[103] *Id.* at 12.
[104] *Id.* at 16
[105] *Id.*
[106] *Id.* at 14 (internal quotations omitted).
[107] *Id.* (internal quotations omitted).
[108] *Id.*
[109] *Id.* at 16.

Third, the FDA also rejected PROP's proposed distinction for use in opioid labeling between chronic cancer pain, on the one hand, and chronic non-cancer pain, on the other.[110] Specifically, the FDA wrote:

> "All of PROP's labeling change requests are limited to 'non-cancer' pain, a distinction that is not made in current ER/LA opioid analgesic labeling. It is FDA's view that a patient without cancer, like a patient with cancer, may suffer from chronic pain, and PROP has not provided scientific support for why labeling should recommend different treatment for such patients. In addition, FDA knows of no physiological or pharmacological basis upon which to differentiate the treatment of chronic pain in a cancer setting or patient from the treatment of chronic pain in the absence of cancer, and comments to the Petition docket reflect similar concerns. FDA therefore declines to make a distinction between cancer and non-cancer chronic pain in opioid labeling."[111]

In the response, the FDA required some labeling changes, though not to the extent advocated by PROP. For example, the FDA granted the request to remove the term "moderate" from the indication for extended-release, long-acting opioid pain medications.[112] In place of that term, the FDA required applicants to use the following language: "[Name of medication] is indicated for the management of pain severe enough

[110] *Id.* at 9.
[111] *Id.*
[112] *Id.* at 9.

to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate."[113] Likewise, the FDA required additional labeling language "urg[ing] prescribers to weigh carefully whether the benefits of an ER/LA opioid outweigh its serious risks on a patient-by-patient basis."[114] This shows the FDA's recognition of the importance of doctors and other prescribers making decisions about whether to use opioid medications in each individual patient's unique circumstances.

The FDA's responses to Citizen Petitions like PROP's can be useful in revealing the FDA's current thinking about disputed issues regarding drug safety and efficacy. In this case, the FDA's response demonstrated that it stood by its previous determinations on the safety of opioids. It also shows that the FDA rejected several of the core contentions of Plaintiffs and their experts, such as their proposed treatment for chronic non-cancer pain, their proposed restriction on the duration of treatment, and their proposed restriction on the daily dosage.[115]

Another similar example is the FDA's response to a July 20, 2017 Citizen Petition by a group called Pharmaceutical Manufacturing Research Services, Inc ("PMRS").[116]

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[113] *Id.* at 8 (also requiring additional language in "Limitations of Use" section).

[114] *Id.*

[115] In August 2017, PROP submitted another Citizen Petition to the FDA. *See* August 2017 PROP Citizen Petition, Docket No. FDA-2017-P-5396. PROP requested that the FDA remove "ultra-high dosage unit" opioids, arguing that their risks "outweigh their benefits" and that they "should be immediately removed from the market to prevent further harm." *Id.* at 1, 5. On February 28, 2018, FDA responded to PROP's Citizen Petition. *See* February 28, 2018 FDA Response, Docket No. FDA-2017-P-5396. Again, the FDA declined to take immediate action, stating instead that the FDA had "not yet resolved the issues raised in your citizen petition." *Id.* The FDA's refusal to "immediately" remove "ultra-high dosage opioids" from the market indicates that it did not believe that, based on the current science, those medications were not safe and effective.

[116] July 20, 2017 PMRS Citizen Petition, available at https://www.regulations.gov/document?D=FDA-2017-P-4352-0001; FDA Response to July 20, 2017 PMRS Citizen Petition, available at https://www.regulations.gov/document?D=FDA-2017-P-4352-0017.

The PMRS group requested, among other things, that the FDA "[r]efrain from approving all other pending or future applications for opioids indicated for chronic use, including use over 'an extended period of time,' use for 'long-term opioid treatment,' or any other labeling for chronic use."[117] PMRS "contend[ed] that these indications are false and misleading and lack substantial evidence."[118] The FDA considered PMRS's position and "agree[d] that opioid addiction and the resulting overdoses and deaths have created a national crisis," and it "note[d] that the Agency is taking a variety of steps to address this public health concern."[119] Nonetheless, the FDA denied the Petition, stating that it "believe[d] it would be premature to make a determination at this time regarding [PMRS's] specific requests."[120] In denying the Petition, the FDA referred to the ongoing opioid PMRs. *See supra* § VII.B. It stated that, given those pending PMRs, the FDA was "denying [PMRS's] request to take the specified actions at this time insofar as we are continuing to consider, both in the context of application-specific reviews and ongoing PMRs, the issues you raised."[121]

PMRS filed another Citizen Petition in July 2018, to which the FDA responded in December 2018.[122] This Petition asked, among other things, that the FDA stop approving opioid medications with indications for chronic non-cancer pain.[123] Again, the FDA rejected the request of PMRS.[124]

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[117] *Id.*
[118] *Id.*
[119] *Id.*
[120] *Id.*
[121] *Id.* at 4.
[122] *See* December 20, 2018 Response to July 23, 2018 PMRS Petition, Docket No. FDA-2018-P-2851.
[123] *Id.*
[124] *Id.*

As with the PROP Petitions, the FDA's response to these Petitions reflects the Agency's views on these important issues. Its response to the PMRS Petitions, like its response to the PROP Petitions, demonstrates that the FDA does not believe there is sufficient evidence based on the current available research and information to take the steps advocated by PROP or PMRS—which mirror the views of Plaintiffs and their experts here. The FDA's views could change based on later research or information, but this response shows the FDA's current views on these issues based on the science and medical research available at the time. Further, the FDA's receipt of and responses to Citizen Petitions is another example of the ongoing FDA's monitoring and regulation of opioid pain medications.[125]

D. The FDA continually monitors reported adverse events.

As noted earlier in this report, even after a medication is approved, the FDA continues to review the safety of the medication. This continued surveillance includes the review of "adverse drug experience(s)"—often referred to as "adverse events"—that are submitted to the FDA by various sources. Physicians, other healthcare providers, and even patients are encouraged to report suspected adverse events to the manufacturer or directly to the FDA, which then reviews them as part of its ongoing post-approval surveillance. The FDA conducts this surveillance, in part, because not all information regarding the

[125] The National Center for Addiction and Substance Abuse of Columbia University ("CASA")—a group on whose Board of Directors Plaintiffs' proffered expert Dr. Kessler served at the time—also submitted two opioid-related Citizen Petitions, one in October 2007 and another in May 2009. *See* October 25, 2007 CASA Citizen Petition, Docket No. FDA-2007-P-0009; May 15, 2009 CASA Citizen Petition, Docket No. FDA-2009-P-0227. In a June 2013 response, the FDA denied both of CASA's Petitions. *See* June 17, 2013 FDA Response, Docket Nos. FDA-2007-P-0009.

safety and effectiveness of a medication is necessarily known at the time of the FDA's initial approval.[126]

Under 21 C.F.R. § 314.80(b), the holders of each approved NDA and ANDA (among others) must make several types of submissions to the FDA regarding potential adverse events involving their medications. For one, applicants "must report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but no later than 15 calendar days from initial receipt of the information by the applicant."[127] These are often called 15-day reports. In addition, applicants must submit reports of other adverse drug experiences—*i.e.*, those not reported as 15-day reports—quarterly for the first three years after the application is approved and then annually after that.[128] These are commonly known as periodic reports. With respect to both Kadian® and Norco®, Allergan's current and former affiliates have regularly submitted both 15-day reports and periodic reports, as appropriate.

Such real-world information is valuable to the FDA's post-approval surveillance.[129] As this new information becomes available to the FDA, it "reviews the data and evaluates

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[126] *See, e.g.*, FDA Draft Guidance, *Drug Safety Information — FDA's Communication to the Public*, available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm295217.pdf, at 3 ("After drug approval, FDA may learn of new, or more serious or more frequent, adverse drug reactions from, for example, postapproval voluntary or mandatory reporting of adverse drug reactions during use of the drug . . .").

[127] 21 C.F.R. § 314.80(c)(1)(i).

[128] *Id.* at § 314.80(c)(2).

[129] Adverse events, though, are not useful in assessing causation. While adverse event reporting is useful to generate hypotheses, for example, they often lack altogether or even incorrectly report key information or are otherwise unreliable for this purpose. The FDA has been quite clear about the limitations of adverse event reporting in determining causation. For example, the FDA's website states that "there is no certainty that the reported event (adverse event or medication error) was due to the product"; further, "FDA does not require a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event." *See Questions and Answers on FDA's Adverse Event Reporting System (FAERS)*, available at

whether there is an emerging drug safety concern."[130] If there is such a concern, "relevant medical and scientific experts within FDA engage in a prompt review and analysis of available data."[131]

As part of this process, the FDA maintains a database known as the FDA Adverse Event Reporting System ("FAERS") that contains adverse event reports that were submitted to the FDA.[132] The FDA describes FAERS as "a useful tool for FDA for activities such as looking for new safety concerns that might be related to a marketed product."[133] Reports contained in FAERS are evaluated by clinical reviewers at the FDA—namely those in the Center for Drug Evaluation and Research as well as the Center for Biologics Evaluation and Research—"to monitor the safety of products after they are approved by FDA."[134] If the FDA identifies a potential safety concern in FAERS, it conducts further evaluation.[135]

From there, the FDA can take additional regulatory action as appropriate. For example, the FDA might require an update to a product's labeling, restrict the use of a

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https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/default.Htm. Nor can one draw any conclusions from the number, frequency or incidence of adverse event reports: "Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event. There are also duplicate reports where the same report was submitted by a consumer and by the sponsor. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population." *Id.*

[130] *See, e.g.*, FDA Draft Guidance, *Drug Safety Information — FDA's Communication to the Public* at , available at https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm295217.pdf, at 3.

[131] *Id.*

[132] *See Questions and Answers on FDA's Adverse Event Reporting System (FAERS)*, available at https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/surveillance/adversedrugeffects/default.Htm.

[133] *Id.*

[134] *Id.*

[135] *Id.*

medication, communicate safety information to the publication—or even remove a product from the market altogether.[136] For instance, with respect to opioid pain medications specifically, in March 2016 the FDA required a change to the labeling of certain opioid medications—including Kadian®—based in part on FAERS.[137] Specifically, in requiring the disclosure of additional risk information about the "occurrence of adrenal insufficiency in patients following the initiation of an opioid," the FDA wrote that "we have become aware of cases submitted to the FDA's Adverse Event Reporting System (FAERS) similar to those described in the published literature."[138] In that instance, the labels for Kadian® and other opioid medications were revised to provide prescribers additional information on this risk. *See infra* § IX.

At bottom, the reporting and analysis of adverse event information is a crucial tool in the FDA's ongoing surveillance of opioid pain medications, including Kadian® and Norco®.

VIII. FDA WARNING LETTERS

A. Generally

An FDA warning letter is a correspondence that the FDA sends to a regulated entity to notify it of potential violations so that the entity has "an opportunity to take voluntary and prompt corrective action."[139] Warning letters are "informal and advisory."[140]

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[136] *Id.*

[137] *See* March 22, 2016 FDA Letter, ALLERGAN_MDL_02195310.

[138] *Id.* at ALLERGAN_MDL_02195311; *see also id.* at ALLERGAN_MDL_02195310 (also referring to the FDA's search of FAERS to identify cases regarding the "occurrence of serotonin syndrome following the initiation of an opioid in patients who had previously been taking one or more serotonergic drugs").

[139] FDA Regulatory Procedures Manual, § 4-4-1, *available at* https://www.fda.gov/downloads/ICECI/ComplianceManuals/RegulatoryProceduresManual/UCM074330.pdf.

[140] *Id.*